ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 7, Issue – 4, August - 2024, Page No. : 196 – 204

Long-Term Relapse of Nonspecific Ulcerative Colitis in The Extraintestinal Form of Gangrenous Pyoderma

[1]Vasilevsky Vladimir Petrovich, Associate Professor, Department of Surgical Diseases, Grodno State Medical University, Belarus

[2]Obuhovich Anneta Romualdovna, Assistant Lecturer, Department of Surgical Diseases, Grodno State Medical University, Belarus

[3]Warnakulasuriya Fernando Rashina Shanani, Sub-Ordinator, Department of Surgical Diseases, Grodno State Medical University, Belarus

[4]Zhdonets Sviatlana Viacheslavovna, Surgeon – Proctologist, Purulent Surgery Department, Grodno University Clinic, Belarus

[5]Kerimova Sapartach Shirdogdievna, Pathologist, Grodno Regional Clinical Pathology Bureau, Grodno, Belarus

Corresponding Author: Warnakulasuriya Fernando Rashina Shanani, Sub-Ordinator, Department of Surgical Diseases, Grodno State Medical University, Belarus

How to citation this article: Vasilevsky Vladimir Petrovich, Obuhovich Anneta Romualdovna, Warnakulasuriya Fernando Rashina Shanani, Zhdonets Sviatlana Viacheslavovna, Kerimova Sapartach Shirdogdievna, "Long-Term Relapse of Nonspecific Ulcerative Colitis in The Extraintestinal Form of Gangrenous Pyoderma", IJMACR- August - 2024, Volume – 7, Issue - 4, P. No. 196 – 204.

Type of Publication: Case report

Conflicts of Interest: Nil

Abstract

Introduction: Pyoderma gangrenosum is a rare, inflammatory, non-infective, non-neoplastic skin disorder that is commonly associated not only with inflammatory bowel disease but also with various other conditions such as rheumatoid arthritis and paraproteinemia. This report details a case of pyoderma gangrenosum in a patient whose clinical course was correlated with underlying ulcerative colitis. Description of a clinical case. The patient, identified as Patient L., a 72-year-old woman (body mass index – 24.9kg/m2) with non-specific ulcerative colitis presenting as a total, relapsing course with moderate activity according to the Mayo index (9) and showing sensitivity to glucocorticoids, exhibited gangrenous pyoderma on her left leg. The patient received care at the Department of Purulent Surgery at the Grodno University Clinical Hospital in the Republic of Belarus, under the assessment and management of a multidisciplinary team consisting of a dermatologist, an infectious disease specialist, and a surgeon. Comprehensive therapy was promptly initiated during hospitalization and diligently

continued on an outpatient basis, aligning with the patient's clinical status and medical history. Conclusion It is unequivocally imperative to administer effective, long-term treatment for ulcerative colitis to prevent serious complications. The compelling evidence from clinical cases and academic literature underscores the pivotal role of implementing appropriate therapeutic measures in managing disease exacerbations and inducing remission.

Keywords: Extraintestinal manifestations, Pyoderma Granulosum, Ulcerative Colitis

Introduction

Ulcerative colitis is a chronic inflammatory disease affecting the colon, typically found in individuals aged 30-40. It predominantly affects the gastrointestinal, musculoskeletal, ocular, and cutaneous systems, leading to complications outside the gastrointestinal tract known as extra-intestinal manifestations [1]. These manifestations are seen in 5% to 50% of all inflammatory bowel disease cases [2], with 15% being cutaneous manifestations. Common dermatological manifestations include erythema nodosum, pyoderma gangrenosum, sweet syndrome, and psoriasis [3]. Pyoderma gangrenosum is a severe form, and its development in conjunction with ulcerative colitis or Crohn's disease has been reported [4-6]. However, in a study of 86 patients with pyoderma gangrenosum, no direct relationship with ulcerative colitis was found [7]. Treatment typically involves systemic Mesalazine therapy, which has been used for mild to moderate ulcerative colitis. Mesalazine therapy has also been indicated as a treatment for pyoderma gangrenosum [8]. New treatment options include immunosuppressive agents such as cyclophosphamide and azathioprine, used alone or in combination with steroids [9]. Cyclosporine has also been reported as effective in patients resistant to steroid therapy [10]. Further investigation and understanding the pathogenic relationship are crucial to clarify the uncertain connection between pyoderma gangrenosum and ulcerative colitis.

Case Presentation

Patient information

The 72-year-old female patient was admitted to the Department of Purulent Surgery at Grodno University Clinical Hospital on September 1, 2023. She presented with a long-standing non-healing ulcer in the lower third of her left leg, accompanied by localized pain and difficulty walking.

Medical History: In her 40s, approximately 30 years ago, the patient was diagnosed with nonspecific ulcerative colitis. Following intensive inpatient and outpatient treatment (unfortunately, the patient was not able to give a clear view of prescribed medications), she experienced a remission period without reported exacerbations, aside from occasional observation of blood in her stool. After this period, she refrained from seeking medical consultations for over 25 years and did not adhere to maintenance therapy. In February 2023, a painless lump developed on her left lower leg, which progressively led to the formation of necrotic areas. Despite seeking outpatient care with unspecified pharmacological and conservative interventions, her condition deteriorated. Subsequently, from June 14, 2023, to July 4, 2023, she was admitted to and managed in the surgical department of City Clinical Hospital. Following discharge, she experienced a symptom exacerbation requiring readmission to the purulent surgery department of Grodno University Clinical Hospital on September 1, 2023.

Personal History: The patient had a prolonged history of primary hypertension, managed with a daily regimen of bisoprolol (10 mg/day), valsartan (160 mg/day), and atorvastatin (20 mg/day). She did not receive oral anticoagulants or antiplatelet drugs, nor did she encounter acute intestinal infections or outbreaks of infectious diseases. In addition, the patient had no prior surgical history, denied transfusions, and reported no hereditary diseases, detrimental habits, or allergies.

Clinical Findings

The patient was admitted in a stable condition, demonstrating consciousness, and well orientated. She exhibited a normosthenic body type with a body temperature of 36.5°C, a height of 165 cm, and a weight of 68 kg, resulting in a body mass index (BMI)

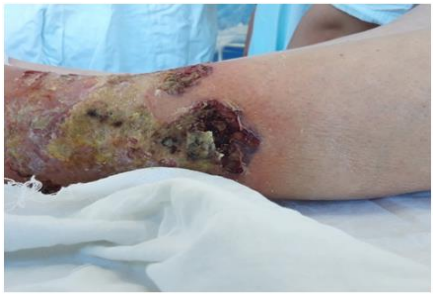

Figure 1: Patient L. left lower one-third of leg with multiple black scabs and ulcers with purulent discharge.

Of 24.9 kg/m^2 Clinical examination revealed elastic, non-enlarged, painless lymph nodes, a respiratory rate of 17 breaths per minute, and vesicular breath sounds on bilateral lung auscultation. Cardiac auscultation revealed clear S1 and S2 heart sounds without murmurs, a rhythmic pulse of 68 beats per minute, and a blood pressure of 130/80 mmHg. Gastrointestinal and urinary systems were unremarkable on admission, with a symmetrical, soft, and non-tender abdomen and audible peristalsis. There were no signs of peritoneal irritation, and normal bowel movements were observed initially. However, on the 9th, 11th, and 12th days of admission, the patient reported frequent loose stools with cherry-colored blood. Subsequently, from the 13th to the 28th day, she experienced low-grade fever, passed stool with mucus and blood up to 6 times daily, and presented with tenesmus. Following the implementation of specific therapy, the patient ceased reporting blood in her stools from the 29th day until discharge, with stool consistency being mushy and blood-free. In the lower third of the left leg, there are circular pigmented areas of the skin with multiple black scabs, along with several ulcers of varying sizes with purulent discharge. The largest ulcer, measuring up to 1.5 cm in diameter, is located on the back surface of the lower leg, and there are multiple ulcers with bluish edges along the lateral and medial surfaces, with the largest one measuring about 5x4 cm (figure 1). The patient's leg veins do not appear contoured when standing.

The primary diagnosis

Ulcer of the lower extremity, not classified elsewhere, Dermatitis, unspecified (main), (01.09.2023) Essential [primary] hypertension (associated).

Timeline

The chronology of the disease in patient L., is depicted on the figure 2.

Diagnostic Assessment

Laboratory investigations (conducted at the Grodno University Clinical Hospital, Belarus on September 1, 2023; reference values are indicated in brackets)Complete blood count: Red blood cells 3.8 x10*12/l (3.7-4.9) x10*12/l; Hemoglobin 112 g/l (120-160) g/l; Leukocytes 14.56 x10*9/l (4-9) x10*9/l; Color index 1.12; Hematocrit 34% (32-47)%; Platelets 326 x10*9l (150-450)x10*9l; MCV (Mean erythrocyte volume) 88.2 Fl (82-92) Fl; MCH (hemoglobin content in erythrocytes) 29.5 pg (28-32) pg; MCHC (erythrocyte

hemoglobin concentration) 33.4 g/dl (32.3-36.5) g/dl; RDW (degree of anisocytosis) 13.5% (11.5-14)%Biochemical blood test: Total protein 71 g/l (65-85) g/l; Urea 5.7 mmol/l (1.7-8.3) mmol/l; Creatinine 87 µmol/l (53-97) µmol/l; C-reactive protein 30.2 mg/l (0-6) mg/l; Total bilirubin 12 µmol/l (5-20.5) µmol/l; Blood glucose 8.7 mmol/l (3.5-6.2) mmol/l; Aspartate aminotransferase 16 U/l (5-37) U/l; Alanine aminotransferase 10 U/l (5-42) U/l; Amylase 38 U/l (25-100) U/l; Sodium 134 mmol/l (130-155) mmol/l; Potassium 3.8 mmol/l (3.2-5.6) mmol/l; Chlorides 98 mmol/l (95-110) mmol/lCoagulation test: APTT SYSMEX 33.3 sec (20.9-30.3) sec; Prothrombin time SYSMEX 11.4 sec (9.7-11.8) sec; Prothrombin activity complex (according to Quick) 88.3% (78.1-123.3) %; INR SYSMEX 1.05 (0.8-1.2); Fibrinogen SYSMEX 4.87 g/l (1.7-4.2) g/lUrine Analysis: Specific gravity 1.01 (1.015-1.025); Nitrites Negative; pH 5 (5.5-7); Color dark

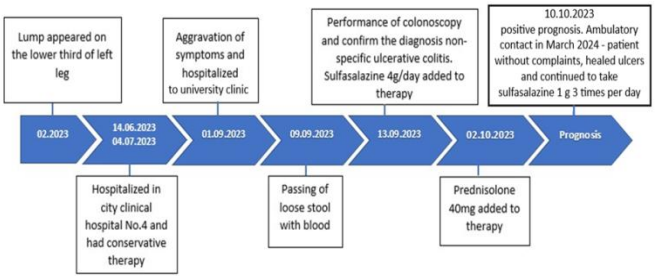

Figure 2: Sequence of disease in patient L., key events and prognosis

yellow; Transparency transparent; Leukocytes 1 number / hpf (<9) number/hpf; Epithelial cells 1 number/hpf (<3) number/hpf; Flat epithelium 1 number/hpf (<9) number/hpf; Mucus 6 number/hpf (<9) number/hpf

Other investigations

Microbiological examination 05.09.2023: Material examined: wound discharge; Isolated microorganisms: Kocuria kristinae; Contamination: 10 *4

ELISA analysis 11.09.2023: Antinuclear antibodies Screen Ig G 0.7 index (0-1) index

ELISA analysis 16.09.2023: Procalcitonin 0.03 ng/ml (<0.1ng/ml)

Flow Cytometry [Biological material Peripheral blood] 26.09.2023: Leukocytes 15.11; Lymphocytes 16.9; CD3+ 77.3% ((58-85)%); CD19+ 16% ((6-17)%); CD3+ CD4+ 58.7% ((30-61)%); CD3+ Anti HLA-DR+ 5.4% ((3-15)%); CD3+ CD8+ 13.9% ((19-35)%); CD3- CD8+ 4.9%; CD8+ Anti HLA-DR+ 1.5%; CD3+ CD16+ / CD56+ 6.9% ((0-5)%); CD3- CD16+ / CD56+ 6.5% ((8-17)%); CD4/CD8 ratio 4.22 ((0.6-2.3)); T lymphocytes 1.97 ((0.6-2.2)); B lymphocytes 0.41 ((0.11-0.53)); CD4+/CD8+ 0.7%; HLA-DR+ 20.3%; total Ig A 4.19 g/l; total Ig M 1.26 g/l; total Ig G 9.0 g/l

Clinical and laboratory conclusion; In the peripheral blood sample under study, the content of leukocytes was 15.11x10\9\l, lymphocytes 16.9%. In the studied population of peripheral blood lymphocytes, the content of total T-lymphocytes is within normal limits, but within the population of total T-lymphocytes there is a decrease in the content of cytotoxic T-lymphocytes, and as a result, the IRI is increased, as well as an increase in the content of killer T lymphocytes. NK content is reduced. The content of

B-lymphocytes is within normal limits. The content of antibodies of classes Ig G, M- is normal, Ig A- is slightly increased.

Instrumental Analysis

Ultrasound of the lymphatic system 05.09.2023 - Inguinal lymph nodes on the left – 33x10mm, 10x5mm, 8x6mm, 7x4mm, 6x4 mm Shape - ovoid Structure unchanged. Popliteal lymph nodes - on the left - not identified.

Esophagogastroduodenoscopy 11.09.2023 -The esophagus and cardia are without features. There is mucus and liquid in the stomach. The gastric mucosa is unevenly hyperemic, with the presence of acute erosions up to 0.1 cm. Peristalsis can be traced in all departments. The folds are completely straightened with air. Pylorus oval, bulb 12 p.c. without features. Conclusion: Erosive gastritis.

Cytological analysis of Esophagogastroduodenoscopy - Helicobacter pylori was not detected. No atypical cells were found.

Rectosigmoid colonoscopy 13.09.2023 - The colon mucosa was examined up to the cecum, then the contents. In the intestinal lumen throughout there is a small amount of mucus and fecal residues. The mucous membrane in the examined areas is clearly diffusely hyperemic, eroded, sharply swollen, with a crimson tint, and an overlay of white fibrin. No oncological pathologies were identified in the examined area. Biopsy was taken from the recto sigmoid region. Conclusion: Endoscopic picture of ulcerative colitis. Microscopic analysis of biopsy collected during Rectosigmoid colonoscopy 13.09.2023 - Erotic mucosa with focal sclerosis, edema, pronounced leukocyte, predominantly lymphoid infiltration. Conclusion: Similar changes can occur with nonspecific ulcerative colitis.

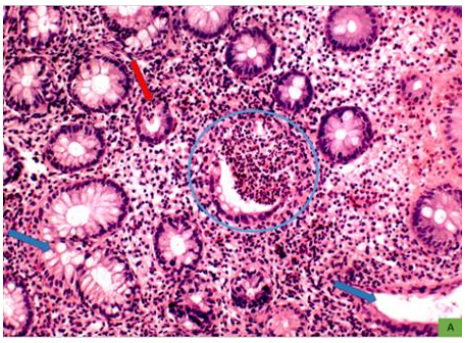

Figure 3: colon mucosa with irregular crypts (blue arrows), the cell population is represented by diffusely arranged plasma cells, macrophages, eosinophils, lymphocytes. The penetration of groups of neutrophils into the surface epithelium with the formation of erosions, abundant neutrophil infiltration of its own plate, as well as into the epithelium of crypts with the destruction of the latter (cryptitis (red arrow); crypt abscesses – 5% / 50% of crypts are involved (blue circle). Staining: hematoxylin and eosin. ×200

Echocardiography 21.09.2023: The aorta, valves of the aortic valve, and the mitral valve are compacted. Hypertrophy of the Inter Ventricular Septum, left ventricle. Mitral valve regurgitation 1 stage. Tricuspid valve regurgitation 1 stage. Aortic valve regurgitation 1-2 stage. Left ventricular diastolic dysfunction (impaired relaxation) Ejection Fraction 71%. Pulmonary pressure syst. 21 mm. Hg.

Rectosigmoid colonoscopy 26.09.2023 - The mucous membrane of the large intestine was examined to the hepatic angle, then to the intestinal contents. There is a small amount of mucus and fecal residues in the lumen; no pathological contents (blood, pus) were detected in the intestinal lumen. The intestinal lumen expands poorly. The mucous membrane in the examined areas is brightly diffusely hyperemic, eroded, sharply edematous, and focally covered with an overlay of white fibrin. Peristalsis is sluggish, haustration is blurred. No oncological pathology was detected. Histology No. 1 mucous membrane of the transverse colon, Histology No. 2 mucous membrane of the descending colon, Histology No. 3 mucous membrane of the sigmoid colon, Histology No. 4 rectum. Considering the nature of the damage to the colon, it is necessary to differentiate this pathology from ulcerative colitis and NSAID-associated enteropathy.

Conclusion

Endoscopic picture of ulcerative colitis. Microscopic analysis of biopsy collected during Rectosigmoid colonoscopy: Erosive crypt-destructive colitis is more characteristic of Ulcerative colitis. According to Geboes Score - 14 points. Nancy score – grade 3. High activity (fig. 3).

- **The final clinical diagnosis**

Nonspecific ulcerative colitis, widespread (total), relapsing course, moderate activity (Mayo index 9), sensitive to 5-aminosalicylic acid (5-ASA) and glucocorticoids, with extra intestinal manifestations in the form of gangrenous pyoderma of the left leg (26.09.2023 /main). Mild iron deficiency anemia (complication of the main one). Erosive gastritis (FGDS dated September 11, 2023) (concomitant). Arterial Hypertension 2 risk 3 (concomitant).

- **Medical Interventions (Therapeutic intervention)**

On the day of admission (01.09.2023), the patient underwent wound culture and biopsy of the largest ulcer after consultation with a dermatologist and infectious disease specialist. A biopsy of a full-thickness skin flap with subcutaneous tissue in the upper corner of the largest ulcer was taken under spinal anesthesia, followed by peroxide and chlorhexidine washing and an ointment bandage. Microscopic analysis of the biopsy taken from the lower third of the left leg ulcer on 21.09.2023 revealed a fragment of the dermis and soft tissues with ulceration, widespread purulent destructive inflammation, and proliferation of endothelium and fibroblasts without inflammatory infiltration. No specific morphological picture indicating vasculitis or tuberculosis was identified (Fig.4).

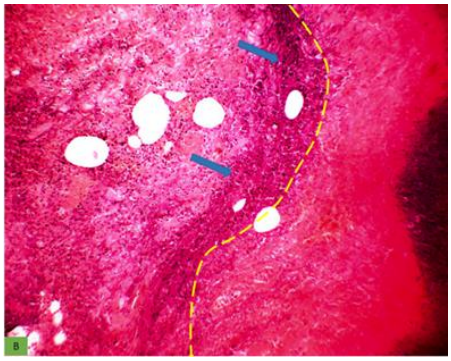

Figure 4: A fragment of dermis and soft tissues with ulceration without epithelial lining with widespread purulent destructive inflammation (blue arrows) and with areas of total necrosis (dotted lines). Staining: hematoxylin and eosin. ×40

The patient was on a regimen of Ampicillin/Sulbactam (sultan) 1.5 g every 8 hours, Emoxypine intravenous drip 0,5% 100 ml 1 time a day, Thiamine + Pyridoxine + Cyanocobalamine + Lidocaine (Borivit) intramuscular 2,0 ml 1 time a day, omeprazole 20 mg in the morning, Perindopril+Indapamide (Co-prenessa) 4 mg/1.25 mg in the morning, aspicard 75 mg at lunch, captopril 25 mg when blood pressure rises above 160/90 and Gabapentin (Gabavest) 300mg 1 time a day as an analgesic in acute postoperative period along with wound care using antiseptics and dressings with mecol-borimed ointment and iodine. The patient remained stable throughout the treatment, with controlled blood pressure and heart rate. On the 5th day, cytological analysis revealed the presence of Kocuria kristinae, at a contamination level of 10 *4, and antibiotics were continued. On the 7th day, a dermatologist was consulted and an ANA blood test and ANCA Screen were planned. Doxycycline 100 mg 2 times a day was added to the treatment. On the 9th day due to the passing of liquid stool with cherry blood, prescribed loperamide 1 tablet 3 times a day, aminocaproic acid solution 250 ml intravenous (IV) drip 2 times a day, and blood count was monitored. The

patient was hemodynamically stable and had a hemoglobin level of 100 g/l which did not indicate emergency blood transfusion. Thirty years ago, the patient was diagnosed with nonspecific ulcerative colitis. Upon suspicion of a recurrence, the treatment included Sulfasalazine at a dosage of 1000 mg per day, along with continued hemostatic therapy and gastro protectors.

Additionally, colonoscopy and laboratory monitoring were ordered, and conservative management of an ulcer on the left lower leg was continued. On the 12th day, Gabapentin (Gabavest) was discontinued due to the emergence of severe general symptoms such as weakness, dizziness, and drowsiness. Following the colonoscopy on 13.09.2023, the dose of sulfasalazine was increased to 4 g orally, Mesalazine suppositories at a dosage of 500 mg twice daily were added to the treatment, and the decision to prescribe glucocorticoids was made based on biopsy results. On the 15th day, Sol. Promedoli 2% - 1.0 intramuscularly was prescribed for adequate pain relief. Prednisolone at a dosage of 40 mg orally was added to the treatment after the biopsy results on 02.10.2023. The patient showed improvement over 4 weeks while taking sulfasalazine. Throughout the treatment, conservative therapy for ulcers was continued using hydrogen peroxide, chlorhexidine, and Mecol-Borimed ointment containing Dioxomethyl tetrahydropyrimidine and Chloramphenicol.

Follow-up and Outcomes: The patient exhibited a positive response to antibacterial treatment and conservative therapy for ulcers, including the use of hydrogen peroxide, chlorhexidine, and mecol-borimed ointment. In addition, the patient responded well to Sulfasalazine 1000 mg and Prednisolone 40 mg, indicating nonspecific ulcerative colitis with extraintestinal manifestations in the form of gangrenous pyoderma of the left leg. Dynamic blood test results are provided in Table 1. Although the patient was stable for the first 8 days, symptoms recurred on the 9th day, leading to a diagnosis of exacerbated nonspecific ulcerative colitis based on complaints, anamnesis, and objective data. With conservative ulcer therapy, progressive healing was observed, with wounds showing reduced necrotic tissue and increased granulation. Upon discharge (fig 5) after 40 days of treatment, the patient was advised to pursue long-term outpatient conservative treatment for ulcers under the care of a gastroenterologist. The prescribed regimen includes sulfasalazine at a dosage of 3 g per day, along with a tapering course of methylprednisolone starting at 24 mg per day for a week, followed by 16 mg per day for a month, and a gradual reduction by 4 mg per day weekly under clinical supervision. Additionally, lansoprazole was advised to be taken at a dose of 30 mg twice daily. The patient is also recommended to undergo dynamic observation of laboratory parameters in the outpatient department and a fibro gastroscopy control in a month. I.

Treatment prospects: The outlook is positive (Fig 6). Medical advice and treatment have been effective in mitigating the worsening of significant symptoms of non-specific ulcerative colitis with extraintestinal manifestations in the form of pyoderma gangrenosum of the left leg. The patient is currently undergoing outpatient treatment and has not required readmission to the hospital since the time of composing this report. III.

Discussion

Numerous studies have indicated a strong correlation between the onset of pyoderma gangrenosum and active ulcerative colitis. In our specific case, the occurrence and recurrence of pyoderma gangrenosum aligned closely with the clinical manifestation of ulcerative

colitis. The onset of gastrointestinal symptoms during hospitalization over the years provided valuable insight linking skin lesions to systemic non-specific pathology. In line with similar cases, pyoderma gangrenosum typically begins as an erythematous pustule or nodule, rapidly progressing to adjacent skin and forming irregular ulcers. The disease

Laboratory Parameters	Reference Range	Days of the disease				
		1st	12th	21st	32nd	39th
RBC, 10^{12}/L	3.7-4.9	3.8	3.76	3.74	3.52	4.21
Hemoglobin, g/L	120-160	112	110	108	102	122
Hematocrit, %	32-47	34	33.4	32.3	31	37.2
Platelets, 10^9/L	150-450	326	454	505	628	593
WBC, 10^9/L	4-9	14.56	17.33	16.43	13.35	15.9
Neutrophils segmented, %	45-70	-	70	61	51	51
Neutrophils band cells, %	1-5	-	10	13	8	7
Lymphocytes, %	18-40	-	10	14	31	31
ESR, mm/h	2-15	-	36	30	-	20
Total protein, g/L	65-85	71	65	58	66	64
Creatinine, mg/dL	53-97	87	77	75	72	74
ALT/AST, U/L	0-40	10/16	30/37	66/68	13/28	15/30
Fibrinogen, mg/dL	1.7-4.2	--	-	-	3.45	3.22
Glucose, mmol/L	3.5-6.2	8.7	5	4.8	5	5.2
CRP, mg/L	0-6	30.2	62	52.6	12	10

Table 1: Blood test laboratory dynamics throughout hospitalization

Note: ALT, Alanine Aminotransferase; AST, Aspartate aminotransferase; CRP, C Reactive Protein; ESR, Erythrocyte Sedimentation Rate; RBC, Red Blood Cell; WBC, White Blood Cell.

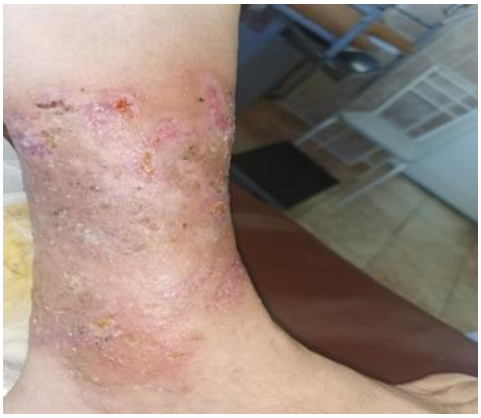

Figure 5: The view of the damaged leg of patient L., upon discharge. Progressive healing in the left lower one-third of the leg following consecutive treatment for ulcerative colitis and local conservative therapy.

adjacent skin and forming irregular ulcers. The disease 's clinical progression is marked by distinct stages, confirmed by both clinical and laboratory findings. The patient's inflammatory dynamics were mirrored in laboratory parameters.

The hemogram showed leukocytosis with a shift to neutrophils and thrombocytosis during the peak of the disease, indicating a reactive response to the inflammatory process. This was confirmed by an increase in C-reactive protein. Clinical improvement correlated with improvement in laboratory blood parameters, including a decrease in the band shift and C-reactive protein levels, following standard therapy. Although the patient's white blood cell count did not return to normal upon discharge, there was significant healing of the ulcer on the left

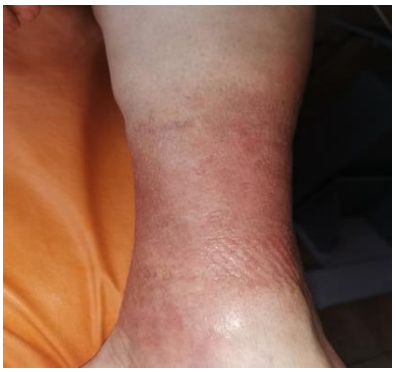

Figure 6: patient L. left lower one-third of leg progressively healing after consecutive treatment of ulcerative colitis for 5 months and conservative therapy of ulcer of the leg. The photos were taken at the moment of dynamic observation of the patient in the outpatient department in March 2024.

Lower extremity with a positive prognosis. The instrumental analysis proved to be valuable in diagnosing the condition. Based on the patient's history and clinical presentation, a rectosigmoid colonoscopy was performed, revealing a sterile culture and diffuse neutrophilic infiltrations with dermolysis upon histopathological examination of the lesion. The patient responded well to standard treatment for ulcerative colitis, including 3000mg per day of sulfasalazine and

40 mg of Prednisolone. After discharge, the patient is currently undergoing conservative treatment and will be evaluated further in the outpatient department. Following medical advice, the patient discontinued Prednisolone on the 20th of February, continues to take Sulfasalazine 3000 mg per day, and is scheduled for regular visits to the outpatient department (figure 6).

Conclusion

The diagnosis and management of nonspecific ulcerative colitis presenting with extra-intestinal manifestations in a patient with primary hypertension and mild iron deficiency anemia is a complex challenge for physicians. The condition may manifest with dermatological symptoms resembling other conditions, necessitating thorough diagnostic procedures based on the patient's comprehensive medical history. Effective management requires decisive actions from a multi-disciplinary team of specialists.

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